DESIGN AND SYNTHESIS OF SOME HETEROCYCLIC MOLECULES TARGETED FOR ANTICANCER ACTIVITY

A

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By

Ms. Wale Risha Rajkumar
M. Pharm.

UNDER THE GUIDANCEOF

Prof. (Dr) Bhusnure O.G.
M. Pharm., Ph.D.

SWAMI RAMANAND TEERTH MARATHWADA UNIVERSITY, NANDED.

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INTRODUCTION: -

Nowadays, cancer is the most terrifying disease affecting the mankind. It is a group of diseases that arise from the abnormal cell growth that has an ability to spread to any part of the body. Research on cancer represents 4% of the whole studies in the world. This area of research expands year after year to include more studies which reflects the global importance of this research area. As cancer is a complicated disorder, there are several difficulties in the treatment process. Many anticancer agents are used alone or in combination with other agents. Understanding the molecular targets, and the cellular proliferation over the past 50 years has triggered the development of over 100 FDA-approved anticancer agents. The earlier anticancer medications as alkylating agents, antifolates, and antimitotic agents were used for treatment of lymphoma and leukemia. These classes of chemotherapeutic agents had a lot of toxic effects with low selectivity and developed resistance. Targeted therapy approach was used to produce more selective, less toxic, and highly effective anticancer agents. Heterocyclic compounds represent the biggest group in the field of medicinal chemistry for treatment of diseases and infections among this group, quinazoline moiety. Quinazoline is a heterocyclic system having two aromatic six-membered rings. One of them contains two nitrogen atoms named as pyrimidine ring and this ring is fused to the second aromatic benzene ring. Therefore, quinazoline is a phenyl pyrimidine compound. Quinazolines have a wide range of pharmacological activities. They are used as anticancer, antiviral, antibacterial, antitubercular, analgesic, antihypertensive, anti-inflammatory, antidiabetic, sedative-hypnotic, antihistaminic, anticonvulsant, and many other uses.

Quinazoline molecules form a favored group of multi acting therapeutic agents in the pharmaceutical and biological fields. The easy preparation and the diverse spectrum of pharmacological activities made this scaffold very important among the different therapeutic agents. Placing different substituents at the 4, 6, and 7-positions of the quinazoline system is the basic approach for the development of novel agents having anticancer activity. Drugs such as Erlotinib, Gefitinib, Afatinib, Dacomitinib, and many other agents are currently used for treatment of different types of cancer such as colon, breast, prostate, and lung cancer. Quinazolines constitute a promising group of anticancer agents active against different types of tumors with an effective therapeutic activity. The majority of quinazolines anticancer research focused onthe mechanistic pathways of their chemotherapeutic action. Most of the quinazoline derivatives having the anticancer activity were found as protein kinase inhibitors. They cause inhibition of replication and transcription of DNA to prevent a tumor growth. Additionally, some of these anticancer derivatives overcome the breast cancer resistance by inhibition of breast cancer resistant proteins. There are other enzymes inhibited by anticancer quinazolines such as thymidylate synthase, poly ADP-ribose polymeras-

1 (PARP), topoisomerase. Therefore, quinazolines exerted their chemotherapeutic activity by various molecular interaction sand mechanistic pathways

It has been known that mutation in the protein kinases leads to impaired signaling, uncontrolled proliferation of cells, and uncontrolled differentiation of these cells. Accordingly, inhibition of tyrosine kinases could be an important biological target in cancer treatment. Most of the quinazoline derivatives having the anticancer activity were found as protein kinase inhibitors. They cause inhibition of replication and transcription of DNA to prevent a tumor growth.

In anticancer drug discovery, heterocycles have played a very important role and have been considered for the development of novel lead compounds. In particular, nitrogen-based heterocycles are a prominent source of biologically active compounds and important structural motifs in anticancer drug design. Indole is one of the most important scaffolds, and the derivatives of it have demonstrated strong ability to induce cell death in a number of cancer cell lines. It is well known that indole derivatives, extensively present in natural compounds and are very important substances in medicinal and biological aspects. The antioxidant effect of indole ring carrier melatonin has been well described. The development of synthetic compounds capable of mimicking the effects of melatonin has progressed considerably during the past decade. These compounds are structurally diverse and ranged from simple indole derivatives and its bioisosteres to phenylalkylamides and constrained melatoninergic agents. Also, indole based small molecule inhibitors targeting the kinase receptors have become a promising option for drug discovery.

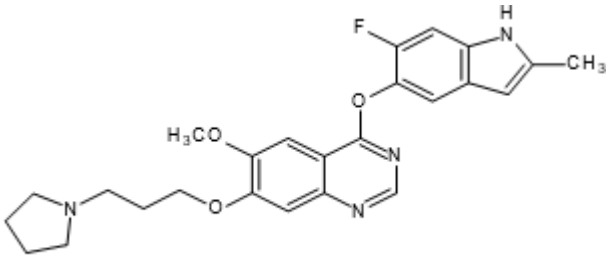
NEED OF STUDY: -

- Cancer research is important because the better we understand these diseases, the more progress we will make toward diminishing the tremendous human and economic tolls of cancer.
- Several anticancer medications that are clinically available are problematically worried about their negative side effects and treatment resistance. Hence, one of the research areas to meet the needs for global health is regarded to be the development of innovative anticancer medicines with desirable effectiveness and minimal toxicities.
- Quinazolines constitute a promising group of anticancer agents active against different types of tumors with an effective therapeutic activity. The majority of quinazolines anticancer research focused on the mechanistic pathways of their chemotherapeutic action. Most of the quinazoline derivatives having the anticancer activity were found as protein kinase inhibitors. They cause inhibition of replication and transcription of DNA to prevent a tumor growth. There are other enzymes inhibited by anticancer quinazolines such as thymidylate synthase, poly ADP-ribose polymeras-1 (PARP), topoisomerase. Therefore, quinazolines exerted their chemotherapeutic activity by various molecular interactions and mechanistic pathways.
- In cancer therapy, Quinazoline derivatives seems to be quite promising and act through various mechanisms that are well established. Quinazoline derivatives can further be explored for the betterment of chemotherapy. A lot of potentials are still hidden, which demands to be discovered for upgrading quinazoline derivatives efficacy.
- The present investigation is mainly focused on the synthesis and QSAR study of new indole based small molecule inhibitors targeting the kinase receptors and protein kinase inhibitory activity of the quinazoline derivatives for better anticancer activity, less side effect and greener synthetic mode.

REVIEW OF LITERATURE: -

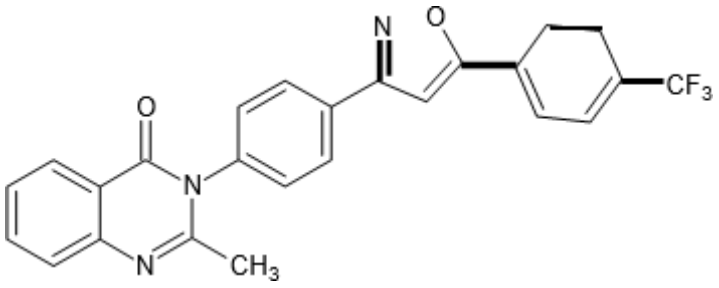
A significant amount of data collected in a literature survey which high lighten the various methods for synthesis of substituted quinazoline by several investigator. The survey also shown quinazoline heterocyclic compound is able to reveal a good potency and anticancer activity.

Mohamed F. Zayed *et. al,* (2023) Quinazolines were used as tyrosine kinases inhibitors for treatment of cancer. A huge frame of scientific experiments proved the efficacy of quinazolines as targeted anticancer agents. Most modifications performed on quinazolines were carried out via changing the substituents at C-4, C-6, and C-7 from the quinazoline system to develop the anticancer activity. Small molecular changes in the quinazoline system led to dramatic changes in the selectivity, the potency, and the anticancer activity. This article presents a clear perspective and a good understanding to scientists and chemists aiming toward development of quinazolines as targeted chemotherapeutic agents. Cediranib is a quinazoline-based marketed anticancer agent having an indole-ether moiety joined to the quinazoline system at the 4-position. It inhibits VEGFR-TK.

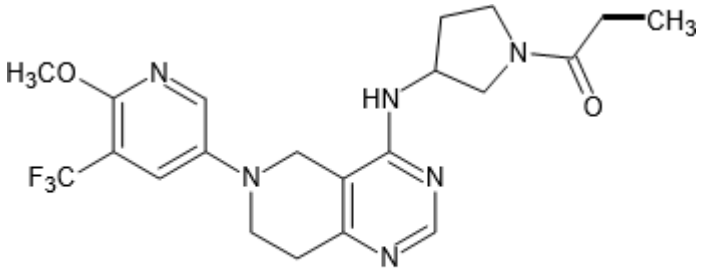


Cediranib

MohamedF.Zayed *et.al,* (2022) The quinazoline system has a wide range of biological activities, such as being analgesic, anti-inflammatory, anti-diabetic, anti-hyperlipidemic, antihypertensive, anti-bacterial, anti-fungal, anti-viral, anti-malarial, anti-convulsant, anticancer, anti-depressant, and anti-tubercular agents, as well as other activities. Therefore, it has great therapeutic potential for the treatment of different types of diseases and infections.

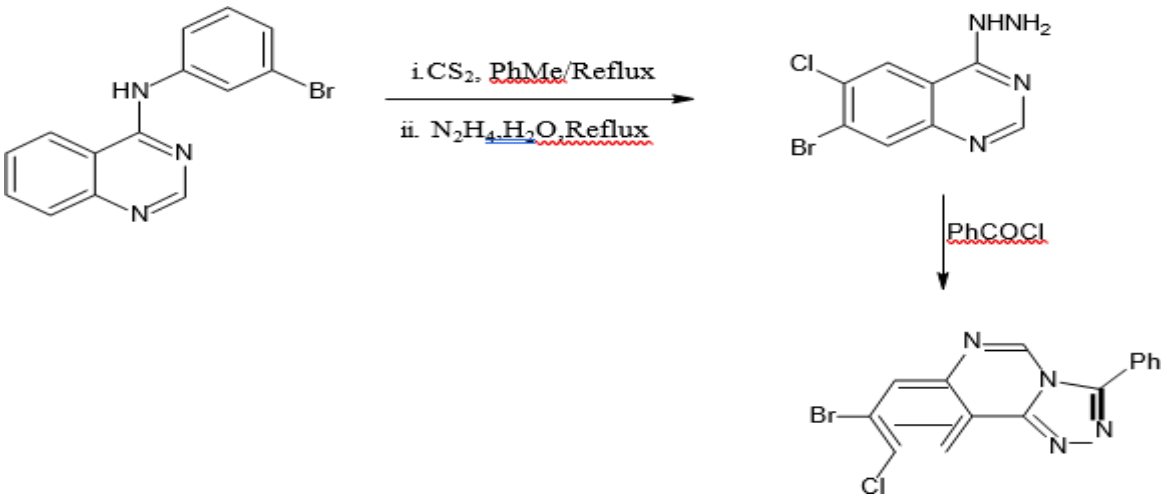


The Analgesic quinazoline

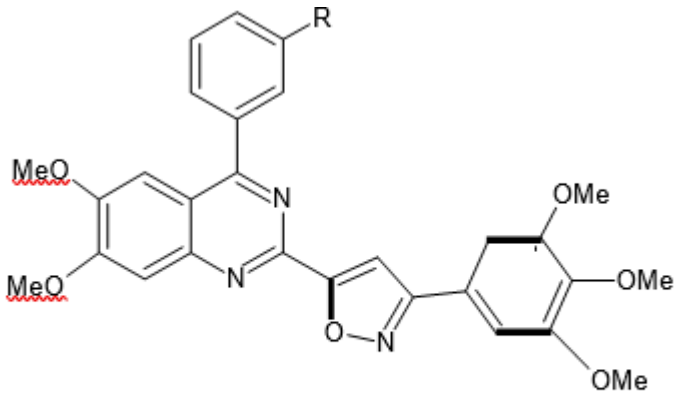


The Anti-inflammatory quinazoline.

Mohamed A. Hawata *et. al*, (2022) The afforded results revealed the effect of incorporation of varied heterocyclic systems with the substituted quinazoline system and the effect of substituents in the newly synthesized 2*H*-pyrimido[1,2-*c*] quinazolin-2-one, the pyrido[1,2-c] quinazoline, the [1,2,4] triazolo[4,3-*c*] quinazoline, and the pyrazolyl-quinazoline hybrids on the anticancer activity. In addition, all the compounds incorporating the latter rings systems showed high cytotoxic effects against the humanbreast cancer cell line **(MCF-7),** which accounts for the importance of incorporating the quinazoline system into other heterocyclic cores such as the pyridine, pyrimidine, and pyrazole rings.

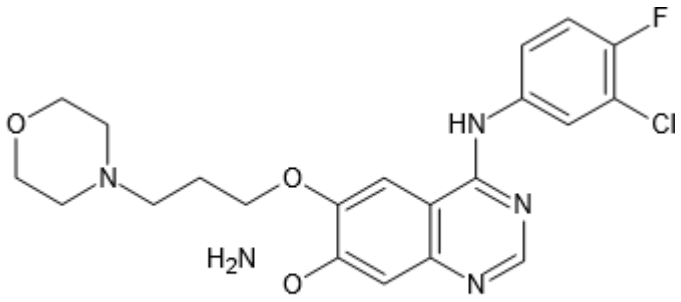


Tasqeeruddin Syed *et. al,* (2021) synthesized a novel series of different aryl-substituted quinazoline-isoxzaole derivatives (12a–j) and their structures were confirmed by spectroscopic techniques. All compounds were examined for their anticancer properties against humanPC3andDU-145(prostate) ,A549(lung)andMCF-7(breast) cancer cell lines by employing MTT analysis with clinical drug as etoposide used as positive control. Among them, compounds 12a, 12b, 12c, 12d and 12j exhibited more potent anticancer activities on all cell lines. All the docked ligands have exhibited good binding interactions with the targeted protein.



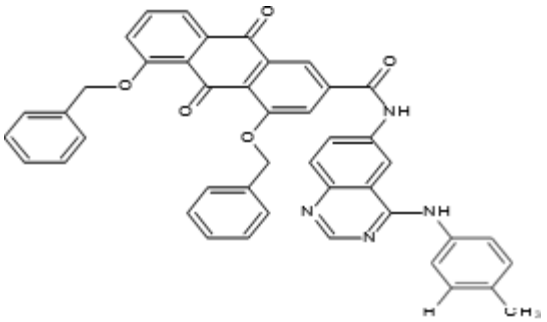
(12a;R=4-methyl,12b;R=4-(dimethylamino),12c;R=3,4,5-trimethoxy,12d;R= 3,5-dimethoxy,12j;R= 2,4,6-trimethoxy)

Vijay Kumar Sharma et. al, (2021) summarizes several synthetic methods for industrial and small-scale quinazoline based anti-cancer drugs. The use of quinazolines for the treatment of various diseases has motivated researchers to improve synthetic approaches and overcome challenges of industrial-scale synthesis. There is a variety of strategies developed for synthesis of such drugs, but the Dimroth rearrangement dominates the synthetic chemistry tool box to produce aminoquinazoline derivatives specifically for industrial scale. The reported synthesis of quinazoline based anti-cancer drugs majorly illustrates the efforts toward efficient and cost-effective approaches which may be utilized for further development or synthesis of novel biologically active derivatives.



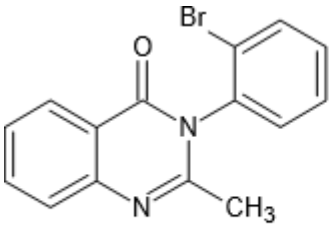
Gefitinib G

Dandan Liang *et. al,* (2019) Collectively, a series of novel anthraquinone–quinazoline hybrids that hit several key targets for cancer therapy were designed and synthesized. Among all hybrids, compound**7d** showed that the strongest antiproliferation activity against A549 cells and exhibited potent inhibitory activities against EGFR; this compound also increased apoptosis, enhanced radiosensitivity, induced DNA damage and possessed multitargeted biological activities. According to results, the novel anthraquinone–quinazoline hybrid**7d**simultaneously acts on multitargets and exhibits excellent anticancer activity compared with the parent compounds; thus, this compound emerges as an anticancer candidate with promising multitargeted biological activities.

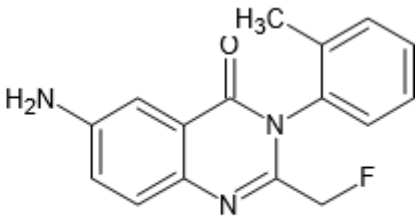


(7d)

Rameshwar S. Chekee*t. al,* (2022) several efforts have been made to represent quinazoline analogs designing, synthesis, and screening for their anticonvulsant potential. From this assess- ment, it appears that quinazoline is an important moiety to com- bat different epileptic seizures and for their treatment. Numerous quinazoline entities displayed potent anticonvulsant potential with higher affinity and lesser toxicity, which can be utilized as a future lead for the development of antiepileptic drugs. A majority of designed quinazoline analogs of this class governed structural alteration of pre-existing lead compounds, whereas some have been designed with the definite objective of modifying targets. The most important fragment of many potent analogues is an amide bond (mainly a benzyl amide ring) and the existence of at least one aryl ring.



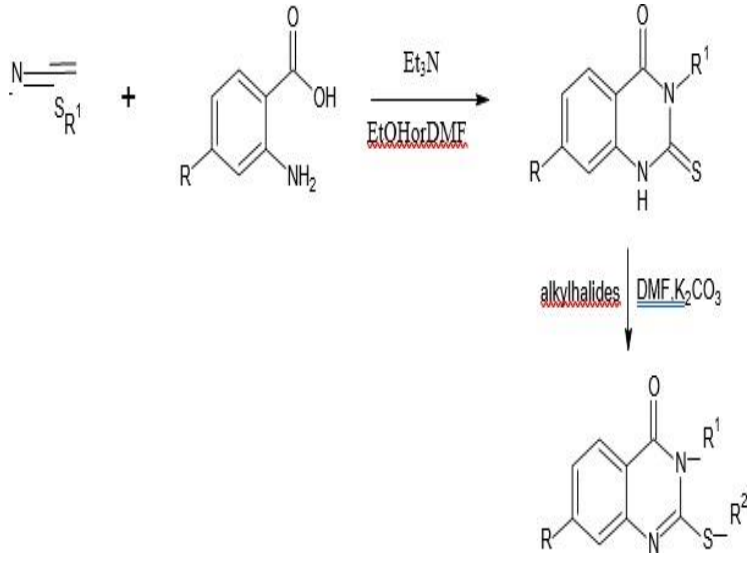
Mebroqualone



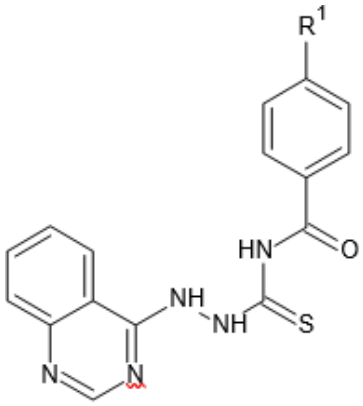
Afloqualone

Hatem A. Abuelizz*et. al,* (2017) tested compounds (1–26) showed good activity against the HeLa and MDA-MB231 cancer cell lines. In particular, compounds 21–23, which had the lowest IC50 values in relation to gefitinib, were identified as the most potent agents that probably active the EGFR-TK pathway. The obtained remarkable and significant cytotoxicity effects of compounds 21–23(IC50rangeof 1.85–2.81 lM) using aromatic and hetero substituent of the quinazoline core could be considered as

useful template for future design and further derivatization or modification to obtain more compounds with potentcy to toxic effects.



JunboHe *et. al,* (2012) have designed and synthesized novel series of quinazoline derivatives containing thiosemicarbazide moiety. Five human cancer cell lines were used to measure cytotoxic activity of the synthesized quinazoline derivatives. The preliminary investigation showed some compounds displayed higher activity against all five human cancer cell lines than5-FU. From the structure activity relationships, it was found that unsubstituted quinazoline ring and benzene ring or halogen substituted benzene ring in quinazoline derivatives 5 and 9 would be the most favorable for their antitumor activity.



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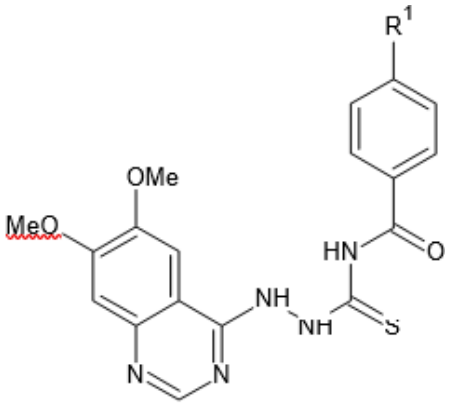
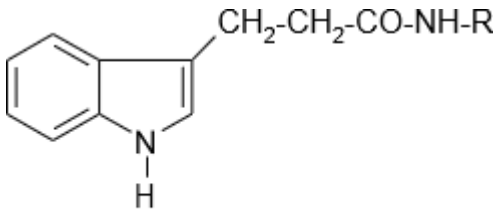


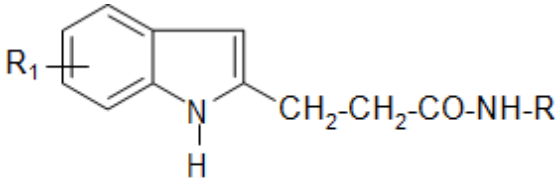
(9)

Zeynepates A*et al,* have carried out a comparative study and evaluation of Melatonin and Indole 3-propronic acid derivatives (v) which shows good biological activity.



(v)

Gilberto S*et al,* have synthesize and structure active relationship for a novel 2-(N-acylaminoethyl) indole (vi) with melatonin –like cyto protective activity.



(vi)

OBJECTIVES OF STUDY: -

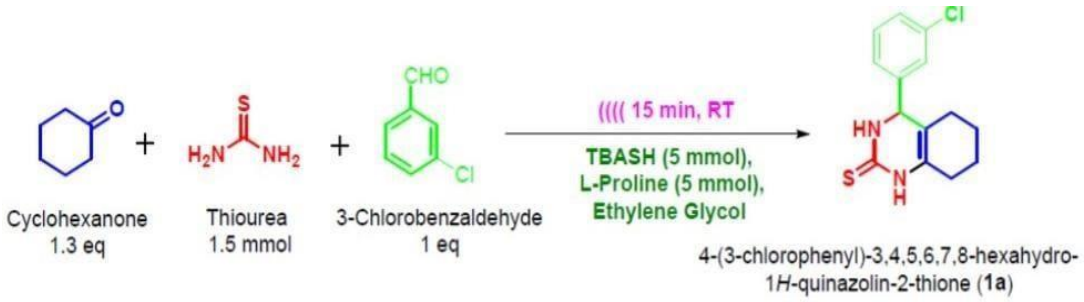
The present work is undertaken with the following objectives:

1. To synthesize novel molecules targeted for anticancer activity.
2. To establish the structure of synthesized novel compound based on chemical and spectral data.
3. To carry out QSAR studies in order to optimize the structure for further development.
4. To carry out the Pharmacological screening of synthesized compound (In *Vivo* animal study/ *Vitro* study.)

MATERIALS &METHODS: -

Proposed Synthetic Pathway:-I

The process of condensing cyclohexanone, thiourea and aromatic aldehydes in the presence of TBASH, L-Proline catalysts under the environment benign conditions (green solvent ethylene glycol)



Proposed Synthetic Pathway: -II

A Substituted indole 3-aldehyde (I) refluxed with hydrazine to yield a product of hydrazide substituted indole (II), then hydrazide substituted indole is heated with chloro ethyl acetyl chloride as result gives Indole intermediate compound (III), then it is further reacted with substituted 2-amino benzothiazole gives novel heterocyclic compound (IV) . A hydrazide substituted indole (II) refluxed with chloro acetyl chloride then formation of intermediate compound (V), which is later reacted with substituted 2- amino benzothiazole, gives series of new heterocyclic compound (VI)

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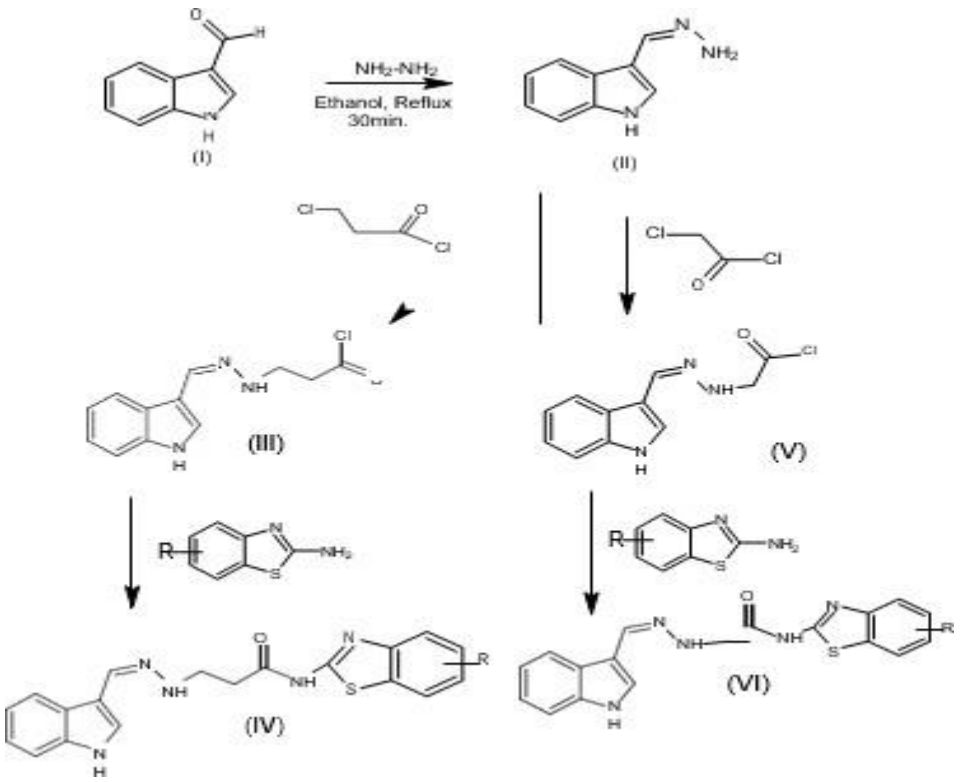
NH2-NH2
Ethanol, Reflux
30min.
(I)
(II)
(III)
(IV)
(V)
(VI)

Characterization of synthesized compounds:

By Chromatographic & Spectroscopic Techniques

Chemicals and other reagents will be collected from standard companies. The compounds will be synthesized. The product will be purified by chromatographic technique column chromatography, preparative chromatography.

The chemical structure of the synthesized compounds is established on the basis of Physical, chemical and analytical data, melting point of synthesized compound is determined in one capillary tube and is uncorrected. They expressed in degree centigrade.

The selected synthesized compounds will be characterized by UV, IR, NMR and Mass spectral data. This will be collected by sending the sample to other advanced Research Centre like NCL, Pune.

The main objective of the present investigation is to explore newer heterocyclic molecule with potent anticancer action.

QSAR Investigation: -

1. To carry out QSAR studies for optimizing structure active relationship of functional groups present in a leading structure in terms of their biological endpoint.
2. Quantitative structure activity relationship (QSAR) is an attempt to correlate structure descriptor of molecule with their physicochemical properties and biological activities.
3. Docking is a tool used in computational drug design predicting whether a particular compound will be a good inhibitor of particular protein.
4. QSAR studies use to reduce the time and money for drug design.
5. QSAR currently are being applied in many disciplines, with many pertaining to drug design the main step implicated in this method include data collection, molecular description selection and procurement, correlation model development and finally model evolution.
6. To understand the relationship between structure and biological activity, for synthesized ring substituted derivatives a QSAR analysis will be carried out by generation of any possible QSAR model.
7. The QSAR investigation will be carried out by VLIFE, Schrödinger and other suitable software.

Pharmacological Investigation: -

The anticancer drugs in current are mostly associated with excessive organ toxicity, lack of cell specificity, short circulating half-life, angiogenesis, metastasis, and a noticeable tendency to induce resistance in the target cells. Hence, to save the lives of millions of people globally, continuous efforts are being made to develop effective anti-cancer drug candidates with minimal side effects. So, our aim studies to screen the synthesized compound for anticancer activity by using a suitable Pharmacological Model (In *Vivo* animal study/*Vitro* study). It is way to explore the synthesized compound for good Pharmacological activities.

Significance of Study:

Cancer is a large group of diseases that can affect any organ or body tissue due to the abnormal cellular growth with the unknown reasons. Many of the existing chemotherapeutic agents are highly toxic with a low level of selectivity. Additionally, they lead to development of therapeutic resistance. Hence, the development of targeted chemotherapeutic agents with low side effects and high selectivity is required for cancer treatment. Quinazoline is a vital scaffold well-known to be linked with several biological activities. The anticancer activity is one of the prominent biological activities of this scaffold. Several established anticancer quinazolines work by different mechanisms on the various molecular targets to present different features of medicinal chemistry as drug design, structure activity relationship, and mode of action of some targeted anticancer quinazoline derivatives and to give comprehensive attention on the chemotherapeutic activity of quinazolines in the viewpoint of drug discovery and its development. It also provides panoramic view for supporting the efforts to design and synthesize novel quinazolines as targeted chemotherapeutic agents.

Scheme for proposed research work: -

Sr. No	RESEARCH WORK	TENTATIVE TIME IN MONTH
1	Literature Survey	03
2	Design of New compound & synthesis Planning	02
3	Procurement of drug, Chemicals and setting up the method for synthesis of title compound.	01
4	Synthesis of newer compound through VLIFE, Schrodinger QSAR suggestion	16
5	Purification and characterization of the new synthesized compounds A. Melting point determination B. Determination of IR, Mass and NMR spectra. C. Elemental analysis	03
6	QSAR investigation	03
7	Pharmacological evaluation of synthesized drug	05
8	Completion of research work and thesis writing	03

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Ms. Wale Risha Rajkumar
Research Scholar
Channabasweshwar Pharmacy College, Latur

Dr. Bhusnure O.G.
Research Guide
Professor and H. O.D.
Channabasweshwar Pharmacy College, Latur

Prof. Dr. Bhusnure O.G.
M. Pharm., Ph.D.
Professor & Head, Dept. of Quality Assurance
Channabasweshwar Pharmacy College
Latur (MS.), India